

AFOSR Final Performance Report

Project Title: Animal Models of Jet Lag

Award Number: FA9550-08-1-0149

Start Date: February 1, 2008

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I. Status of Effort

Our research program specializes in the longitudinal monitoring of pineal melatonin secretion for weeks at a time to decipher mechanisms of circadian pacemaker entrainment and reentrainment in freely moving animals. More specifically, we aimed at understanding circadian pacemaker behaviors following advance shift of the light:dark (LD) cycles, which simulate human jet lag behaviors following eastward travels.

II. Experimental approach

Our longitudinal measurements of melatonin secretion are based on the pineal microdialysis coupled with online HPLC method published a while ago (Figure 1). We have obtained sufficient funding from AFOSR to obtain additional instruments to allow simultaneous monitoring of melatonin secretion from 20 rats at 20 min bins.

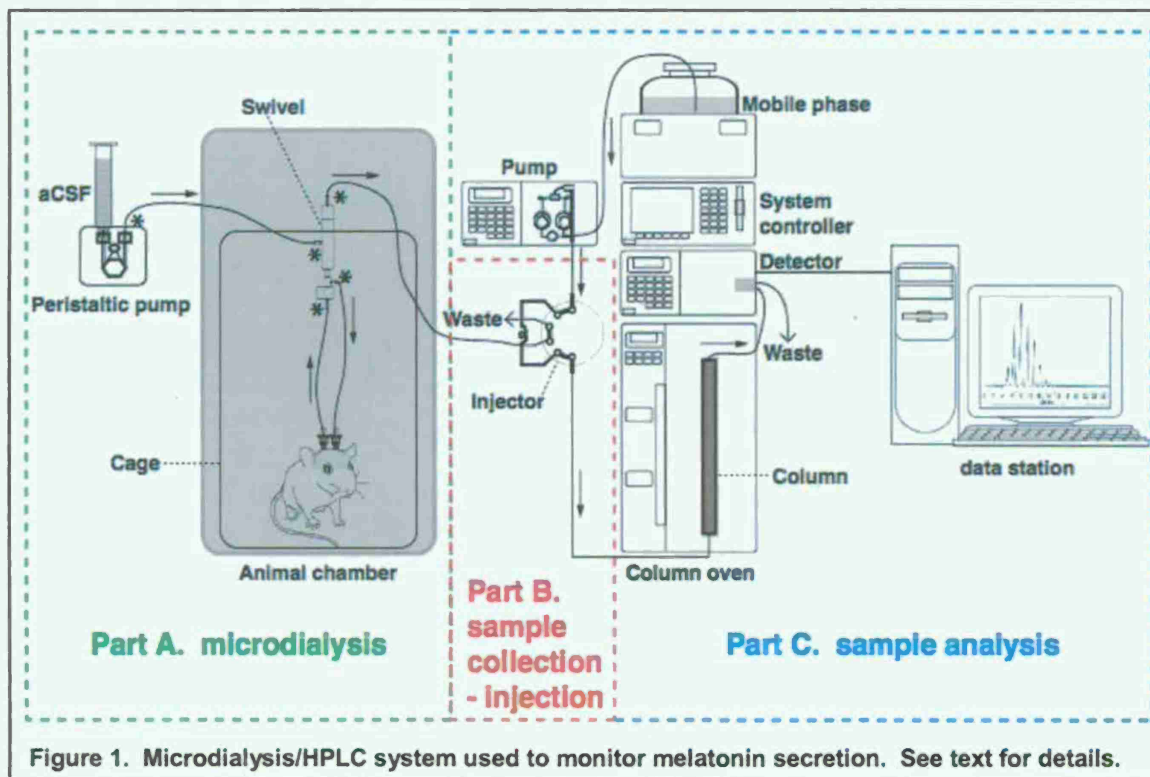


Figure 1. Microdialysis/HPLC system used to monitor melatonin secretion. See text for details.

Part A is consist of a rat housed in their light-controlled chamber with a microdialysis tubing surgically inserted into the pineal gland and connected to a peristaltic pump that delivers saline solution at low rate and to a outlet tubing that delivers pineal dialysates to the sample loop in the actuator in part B. A swivel is placed between inlet and outlet to prevent tubing from entanglement and to allow free movement of rats. Part B is consist of a actuator valve (10 ports/2-positions) used for real time collection and injection of pineal dialysates into the HPLC column. Par C is a set of HPLC instruments that, when put together, allow real time analysis of collected pineal samples. Part C is consist of a HPLC column oven that keeps column temperature constant, an HPLC pump that delivers the collected pineal sample to the column for separation using mobile phase and high pressure, and a fluorescence detector that analyzes pineal samples separated

from the column that emit fluorescence at defined wavelength. Results are sent to the computer for automated analysis using HPLC software.

Publications acknowledging AFOSR support resulting from this grant

1. "N-terminal residues regulate proteasomal degradation of AANAT". Zheping Huang, Tiecheng Liu, and Jimo Borjigin, *Journal of Pineal Research*. 48(3):290-6, 2010.
2. "Circadian Regulation of Pineal Gland Rhythmicity", Jimo Borjigin, L. Samantha Zhang, Anda-Alexandra Calinescu, *Molecular and Cellular Endocrinology*, invited review (peer reviewed). In press, 2011.
3. "Dynamic Relationship between Circadian Melatonin and Per1 Rhythms Following a Shift of the Environmental Cycle", Jimo Borjigin, Mamoru Nagano, L. Samantha Liang, Tiecheng Liu, Michelle Smith, Victoria Booth, Yasufumi Shigeyoshi, Being reviewed by the *Journal of Biological Rhythms*, May, 2011.
4. "Transsynaptic activity-dependent regulation of axon branching and neurotrophin expression *in vivo*", Anda-Alexandra Calinescu, Tiecheng Liu, Michael M. Wang, Jimo Borjigin, Being reviewed by the *Journal of Neuroscience*, May, 2011.
5. "Expansion of melatonin secretion duration in short photoperiod depends on the direction of dark extension in rats", L. Samantha Zhang, Tiecheng Liu, Abeer Khurram, Jimo Borjigin, manuscript ready to submit to *Journal of Biological Rhythms*, May, 2011.
6. "The dark side of light: A single exposure to light at night causes silent 'jet lag'", Mamoru Nagano, Tiecheng Liu, L. Samantha Zhang, Yasufumi Shigeyoshi, and Jimo Borjigin, manuscript in preparation for *Nature*, June, 2011.

Personnel Supported by this grant:

Graduate Students:

L. Samantha Zhang (4th year Neuroscience PhD candidate)

Post-doctoral associates:

Dr. Asamanja Chatteraj (now an assistant professor in India)

Dr. Anda-Alexandra Calinescu (now on her 2nd year in the lab)

Senior Research Associates:

Dr. Tiecheng Liu

Tiecheng Liu carried out all surgical implantation of pineal microdialysis probes and implantation of telemetry transmitters. In addition, Tiecheng performed all microdialysis/HPLC studies and part of primary data analysis. Samantha performed some primary data analysis and all secondary data analysis. Since Alexandra joined us in late 2009, she has also been helping out with some of the data analysis and is in

charge of all molecular studies. The entire team has worked seamlessly and produced large amount of data that are ready to be reported.

Inventions and patent disclosures:

There have been no inventions leading to patent disclosures during this period.

Honors and Awards during grant period:

1. **2009:** DURIP (Defense University Research Instrumentation Program) grant from the Air Force (for equipment only)-FA9550-09-1-0352; *Mathematical Modeling of Circadian Light Response*; 0% effort, Principal Investigator Jimo Borjigin, 04/15/09-03/14/10 (Total cost \$223,572).
2. **2010:** Gilmore Fund for Sleep Research and Education; *Enhancing recovery by treatment of sleep disturbances after stroke: A preclinical study*, 0% effort, Co-PI Jimo Borjigin, 01/01/11-12/31/14 (Total cost \$15,000).

Invited Lectures during the grant period:

2011

Systems Biology Symposium, University of Michigan. *Refining the Art of Entrainment*, 04/04/11.

2010

Neuroscience Graduate Program Fall Retreat: *Mentoring Graduate Students*, 10/02/10.
Department of Neurology, University of Michigan. *Circadian pacemaker dynamics: lessons from melatonin*, 10/15/10.

Department of Psychology, University of Michigan. *Early birds rule! What melatonin reveals*, 12/07/10.

2009

Department of Psychology, School of Education, Inner-Mongolia Normal University, *Comparative analysis of China, Japan, and USA education systems: personal perspectives*, 06/27/09.

Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Beijing University Health Science Center. *Light as a polluter to the circadian timing system*, 07/03/09

Department of Cell and Neurobiology, Keck School of Medicine, University of Southern California. *Clock debt: light as a polluter to the circadian timing system*, 04/28/09

2008

Department of Molecular Pharmacology, Northwestern University Feinberg School of Medicine. *Clock debt: light as a polluter to the circadian timing system*, 12/03/07.

Division of Sleep Medicine, Harvard Medical School. *Circadian Pacemaker Entrainment*, 07/28/08.

FASEB Summer Research Conference - Melatonin Receptors: Actions and Therapeutics. *Pineal melatonin as a marker to assess circadian pacemaker phase*, 08/10/08-08/15/08.

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